REMARKS

The claims have been amended to more clearly describe the invention.

Claim 1 has been amended by using active language to describe the various steps of the method and to more clearly identify various components. Support for the amendments to claim 1 can be found in the Specification on page 1, lines 6-9 and page 6, lines 5-7 and lines 21-23.

Claim 9 has been amended to indicate that the protein-nucleic acid interaction is a Gene32 protein-nucleic acid linking. Support for this amendment can be found in the Specification on page 9, lines 24-26.

Claims 20 and 21 have been amended by deleting the preferred range. The preferred ranges have been introduced into new claims 24 and 25, respectively.

The remaining claims have been amended to reflect the language used in claim 1 and to remove multiple multiple dependencies.

New claim 26 has been added, which find support in the Specification on page 10, lines 8-9 and page 11, lines 23-24.

New claim 27 has been added, which finds support in the Specification on page 9, lines 27-30.

New claims 28 and 29 depend from claims 26 and 27.

No new matter has been added.

Claim Objections

The Examiner has objected to claims 7-21 as being in improper form regarding multiple dependencies.

Applicants have amended the claims to remove the multiple multiple dependencies, thereby overcoming the objection.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-22 as being indefinite for the recitation of "each probe," contending that it is unclear what probes are referred to. The Examiner also indicates that the claims require nucleic acid molecules and nucleotide base sequences and do not set forth probes.

Applicants have amended the claims to indicate that at least one target nucleic acid molecule is hybridized with a set of probes comprising different nucleotide base sequences. Thus, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claim 9 as indefinite for the recitation "Gene32- nucleic acids linking," contending that it is unclear what Gene32 is. The Examiner acknowledges that the art teaches a T4 phage Gene32, but indicates that the art also teaches a variety of newly discovered genes that have been designated Gene32. Applicants respectfully traverse.

Applicants have amended the claim to read "Gene32 protein." The term "Gene32 protein" has a specific meaning to the skilled artisan working in this field. The Gene32 protein is a single-stranded DNA binding protein which is required for T4 DNA replication, recombination and repair. It binds cooperatively to single-stranded DNA and also binds to single-stranded RNA. Gene32 protein has been widely used in studies of DNA-protein interactions and for marking regions of single-stranded DNA and cytological preparations

viewed by electron microscopy. In addition, on a primed single-stranded DNA template, the addition of Gene32 protein results in an increase in the rate of synthesis by T4 DNA polymerase. Gene32 protein has also been shown to be effective in stimulating PCR and to enhance yield and processivity in RNA amplifications.

When used in the context of replication and protein-nucleic acid interactions, the term "Gene32 protein" is understood to mean the T4 Gene32 protein, as evidenced by the use of the term "gene-32 protein" in Karpel (2002) IUBMB Life 53:161-6, Kim et al. (2005) Mol Microbiol 55:1502-14 and Villemain et al. (2000) J Biol Chem 275:31496-504. As a consequence, in the protein-nucleic acid binding context as used herein, the fact that there may be newly discovered genes which have been designated "Gene32" would have no effect on the skilled artisan's understanding that "Gene32 protein" refers to the T4 Gene32 protein. In view of this, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 20 and 21 as indefinite over the recitation "preferably." Applicants have removed the preferred ranges from these claims and have introduced them in new dependent claims, thereby overcoming the rejection.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1-9 and 15 as being anticipated by Tang et al. The Examiner contends that Tang et al. teach a matrix-assisted laser desorption/ionization mass spectrometry of immobilized duplex DNA probes. The Examiner's extensive remarks

regarding the Tang et al. reference can be found on pages 5 and 6 of the Office Action and are not repeated here.

Briefly, the Examiner states that specifically Tang et al. teach that streptavidin-coated magnetic beads were used and biotinylated single-stranded DNA was added to the mixture before removing the supernatant containing unbound oligonucleotides. The magnetic beads were washed and then compacted with complementary oligonucleotides to allow hybridization. After annealing, the supertanant with excess ligand were removed and the beads were washed. The Examiner also contends that Tang et al. teach that preparation of duplex DNA on CPG beads which includes using B-cyanoethyl phosphoamidite chemistry. The Examiner goes on to state that Tang et al. teach analyzing the duplex on the beads with a mass spectrometer which employs a nitrogen laser for MALDI. The Examiner states that Tang et al. teach sequencing which can be carried out and paralleled with increased speed and concludes that Tang et al. teach every limitation of the instant claims. Applicants respectfully traverse.

Applicants first point out that claim 1 has been amended to indicate that the target nucleic acid molecule has an unknown sequence. The method according to the invention combines oligo fingerprinting and analysis by mass spectrometry. The method uses a set of probes wherein each probe has a distinct sequence and a distinct mass. This principle is summarized in Figure 1 of the application. The mass spectrum of the hybridized probes permits derivation of the sequence of the unknown target DNA sequence by using this set of probes with distinct sequence and distinct mass, and so a plurality of nucleic acids can be analyzed simultaneously.

Tang et al. do not anticipate the present invention. First, Tang et al. used a known sequence as a target and also used probes with known sequences (See Figure 2 (a) and (b). Here, Tang et al do not use any unknown sequence as the target. Instead, Tang et al. use a known sequence as the target and manufacture known sequences that are either shorter or longer than the known target and which contain a complementary sequence.

Second, Tang et al. do not teach that each probe used in the reaction must have a distinct mass that will allow identification of the associated sequence. In fact, the final paragraph of the reference suggests that this is not necessary at all. Here, Tang et al. state that genomic DNA can be digested into small fragments and used in hybridization reactions with immobilized probes having known sequences. Such DNA digestions will produce a large number of nucleic acid molecules with the same number of nucleotides, but having different sequences. Likewise, Tang et al. teach that the immobilized probes provide all possible five base single-stranded 3' overhangs, suggesting that the same number of nucleic acid bases is present, but the associated sequences differ.

The mass of a DNA molecule, however, is only dependent on the total number of each base present in the sequence; that is, the particular number of A, T, C and G bases present. The mass is not associated with the particular arrangement of those bases in the sequence. To illustrate, a 24 base nucleic molecule containing four bases each of A, T, C and G will have the same mass no matter whether the sequence is AAAATTTTCCCCGGGG, ATATCGCGATATCGCG, ATCGATCGATCGATCG, or etc. Using the Tang et al. approach, if one or more of these sequences was detected by a mass spectrometer, it would be impossible to distinguish which of these molecules was present without further sequencing. Yet in the present invention, it is required that each probe used,

regardless of the number or origins of the probes, have a unique mass, thus allowing identification of the probe's sequence without further manipulation.

Furthermore, the instant invention requires that the unknown target molecules are immobilized, whereas in the final paragraph of the Tang et al. reference it is the probe sequences which are immobilized.

As a consequence, Tang et al. do not teach at least one of the critical elements of the instant invention, that each probe must have a unique mass compared to all other probes in the reaction and that the target sequence is unknown. As such, the Tang et al. reference cannot support an anticipation rejection since Tang et al. do not teach each and every element of the claims. In addition, the final paragraph of the reference also suggests that simultaneous analysis of a plurality of nucleic acids is only possible in conjunction with primer extension and Sanger sequencing in contrast to the instant invention which does not require any further reaction in order to elucidate the target sequence. As a consequence, Applicants respectfully request reconsideration and removal of the rejection.

The Examiner has rejected claims 1-22 as being anticipated by Van Ness et al. The Examiner contends that Van Ness et al. teach a method of gene expression analysis which involves parallel measurement of hybridization with spectrometry. The Examiner writes an extensive interpretation of the Van Ness et al. reference which appears on pages 6-9 of the Office Action and are not reproduced here. Applicants respectfully traverse.

Applicants point out that the main claims of the present invention relate to a method wherein the probes being used each have a distinct individual mass. This novel feature is not disclosed or suggested by the Van Ness et al. reference. The Van Ness et al.

reference relates to nucleic acid molecules which throughout the process carry tags and where the method comprises the steps of cleaving the tags from the probes and subsequently detecting the tags (see column 2, lines 46-47 and 62-63; column 54, line 46-47; column 4, lines 41-47 and column 6). Thus it would be evident to the skilled artisan that the cleavage of the tags from the probes and the detection of the tags (as opposed to the detection of the probes themselves) is a key feature of the Van Ness et al. invention.

Applicants recognize that independent claim 27 and dependant claims 10 and 12 further specify that the probes carry a tag. There is, however, no disclosure, suggestion or teaching in the Van Ness et al. reference to exclude or eliminate the step of cleaving the tags from the probes, nor of the complete omission of the tags. On the other hand, the skilled artisan after reading the present Specification would conclude that the method according to the present invention does not extend to the mass spectrometrical analysis of tags, but instead relates to the mass spectrometrical analysis of the probes, which according the invention consist of nucleic acids. See step (d) of claim 1 and page 5 of the Specification.

The analysis of the probe, rather than the tag, is underscored by the working examples presented in the instant Specification. For example, Example 2 deals with a charge tagged PNA library and specifically states that the probe, not the tag, is analyzed.

In view of the above, the Applicants submit that the present claims are directed to patentable subject matter.

Conclusion

In view of the above remarks, all of the claims remaining in the application as amended, including newly added claims, are submitted as defining novel, non-obvious and patentable subject matter.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at telephone number 714-708-8555 to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R §§ 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a response in connection with the present application and authority is given to charge Deposit Account No. 02-2448 the required fee of $ 510.00.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Attachment(s): Karpel
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